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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/802,970	03/16/2004	Carl-Magnus A. Andersson	ACADIA.014C2	5078

20995 7590 01/25/2008

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EXAMINER	
MABRY, JOHN	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
01/25/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/802,970	ANDERSSON ET AL.	
	Examiner	Art Unit	
	John Mabry, PhD	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,53-60 and 78-88* is/are pending in the application.

4a) Of the above claim(s) *15-49 and 66-78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,53-60 and 78-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :8/9/07, 5/23/07, 4/23/07, 3/20/07, 3/14/07, 3/29/06, 1/23/06, 6/18/04.

DETAILED ACTION

Examiner's Response

Applicant's response on filed December 21, 2007 in response to the Election/Restriction dated October 25, 2007 has been received and duly noted. The Examiner acknowledges Applicants' election of Group I with traverse. The Applicant respectfully requested the addition of the variables Ar1 and Ar2 which represent aryl and heteroaryl defined by the Specification. Applicant states that the inclusion of said variables, a search burden would not be imposed on the Examiner. Examiner respectfully disagrees. Proof of search burden is illustrated below in a preliminary STN search – where Ar1 and Ar2, as defined by Specification, yields 258,180 iterations (avg.) and 1,807 projected answers (avg.). However, the Examiner has opened the search of Ar1 and Ar2 to not only to include phenyl (elected Group I), but to include thiophenyl, furanyl, pyridinyl and benzo-1,3-dioxolyl.

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L3      STRUCTURE UPLOADED

=> d l3
L3 HAS NO ANSWERS
L3                STR
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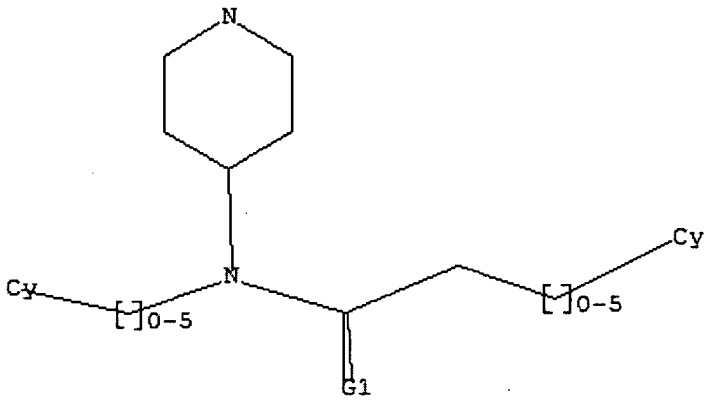


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G1 O,S

Structure attributes must be viewed using STN Express query preparation.


=> s l3 sss sam
SAMPLE SEARCH INITIATED 12:00:10 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -    12909 TO ITERATE

 15.5% PROCESSED     2000 ITERATIONS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       251373 TO   264987
PROJECTED ANSWERS:            1237 TO     2377
```

Thus, the restriction requirement is deemed proper and **FINAL**.

In view of this response, the status of the rejections/objections of record is as follows:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14, 53-60 and 79-88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substituted" in respective claims is a relative terms which renders the claim indefinite. The term "substituted" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The Oxford Dictionary of Chemistry defines the term derivative as a compound that is derived from some other compound and usually maintains its general structure.

Additionally, the term "substituted" has no clear limitations. What does the Applicant intend by this term? Please indicate where in the Specification is there such support.

The term "organyl group" in claims 1-5 is a relative term which renders the claim indefinite. The term "organyl group" is not defined by the claim, the specification does

not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. What does Applicant intend for this term to mean?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14, 53-60 and 79-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for R being oxadiazolyl, imidazolyl, thiophenyl, indenyl, triazolyl, alkyl ester, hydrogen thiazolinyl, benzodioxolyl, benzoimidazazolinyl, alkyl, C3-C6 cycloalkyl, hydroxyl, dioxolyl, and 3-methylquinazoline-2,4(1H,3H)-dionyl, does not reasonably provide enablement for R being **all** substituted and unsubstituted variables as shown below and further defined in the Specification:

> **R is hydrogen, a cyclic or straight-chained or branched acyclic organyl group, a lower hydroxyalkyl group, a lower aminoalkyl group, or an aralkyl or heteroaralkyl group;**

The Specification does not provide any support for said variables at R position. Specification describe starting materials and methods for synthesis of compounds wherein R as aforementioned, but does not describe or list any reagents wherein compounds can be used to synthesis compounds where R as previously described.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims: Scope of the compounds. Owing to the range of many variables, millions of highly substituted azacyclic compounds are embraced.

(2) The nature of the invention: The invention is a highly substituted azacyclic compounds.

(3) Level of predictability in the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and chemical reactivity (which is affected by determinants such as substituent effects, bonding, molecular geometry, steric hindrance, electronic effects, etc) is generally considered to

be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(4) Direction or Guidance: That provided is very limited. Applicant shows a general synthesis of compounds of application's general formula I. The Specification describes starting materials and methods for synthesis of compounds wherein R as aforementioned, but does not describe or list any reagents wherein compounds can be used to synthesis compounds where R as previously described. There is limited evidence in the Specification of the example compounds that only covers no or a small portion of the substituents claimed of formula I. Thus, there is no specific direction or guidance regarding said compounds specifically mentioned in Scope.

The specification does not provide any support for the synthesis of compounds, wherein R being oxadiazolyl, imidazolyl, thiophenyl, indenyl, triazolyl, alkyl ester, hydrogen thiazolinyl, benzodioxolyl, benzoimidazazolinyl, alkyl, C3-C6 cycloalkyl, hydroxyl, dioxolyl, and 3-methylquinazoline-2,4(1H,3H)-dionyl, does not reasonably provide enablement for R being **all** substituted and unsubstituted variables as shown below and further defined in the Specification:

> **R is hydrogen, a cyclic or straight-chained or branched acyclic organyl group, a lower hydroxyalkyl group, a lower aminoalkyl group, or an aralkyl or heteroaralkyl group;**

The availability of the starting material that is needed to prepare the invention as claimed is at issue here...As per MPEP 2164.01 (b). A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to a make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court *in re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made it clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. *In re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

(5) State of the Prior Art: These compounds are substituted azacyclic compounds wherein R = unsubstituted and substituted alkyl, alkylester and hydrogen, which are well documented in the art. So far as the examiner is aware, no substituted azacyclic compounds of general formula I wherein R being **all** substituted and unsubstituted variables as shown below and further defined in the Specification:

> **R is hydrogen, a cyclic or straight-chained or branched acyclic organyl group, a lower hydroxyalkyl group, a lower aminoalkyl group, or an aralkyl or heteroaralkyl group;**

It is not trivial to experimentally interchange any and all of the many substituents and chemical moieties that exist. As described by F. Zaragoza Dörwald, most organic syntheses fail initially and chemical research is highly inefficient due to chemists spending most of their time "finding out what went wrong and why". Therefore, most syntheses of organic compounds are labor-intensive and demanding. Additionally, most final synthetic routes to desired organic molecules are usually very different from initially planned routes. A highly skilled chemist can agree that for many successful organic compounds made, many failures are encountered and experimental repetition is common. This also contributes to the burden and unpredictability of the syntheses of said compounds. (see "Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design" 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Wienheim.

(6) Working Examples: Applicant shows examples (pages 39-129) but no working examples were shown wherein R being **all** substituted and unsubstituted variables as shown below and further defined in the Specification, have been made or used of any kind.

> **R is hydrogen, a cyclic or straight-chained or branched acyclic organyl group, a lower hydroxyalkyl group, a lower aminoalkyl group, or an aralkyl or heteroaralkyl group;**

(7) Skill of those in the art: The ordinary artisan is highly skilled, e.g. a masters or PhD level chemist.

(8) The quantity of experimentation needed: Since there are very limited working examples as described above, the amount of experimentation is expected to be high and burdensome.

Due to the level of unpredictability in the art, the very limited guidance provide, and the lack of working examples, the Applicant has shown lack of enablement for the groups noted.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claims 1-14, 53-60 and 79-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "salts", does not reasonably provide enablement for "prodrugs". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention in the instant case has claims which embrace aryl piperidine compounds. The scope of "prodrug" is not adequately enabled. Applicants

provide no guidance as how the compounds are made more active *in vivo*. The choice of a "prodrug" will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which prodrugs will be suitable for the instant invention.

The instant compounds of formula (I) wherein the prodrugs are not described in the disclosure in such a way the one of ordinary skill in the art would no how to prepare the various compounds suggested by said claims. In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention.

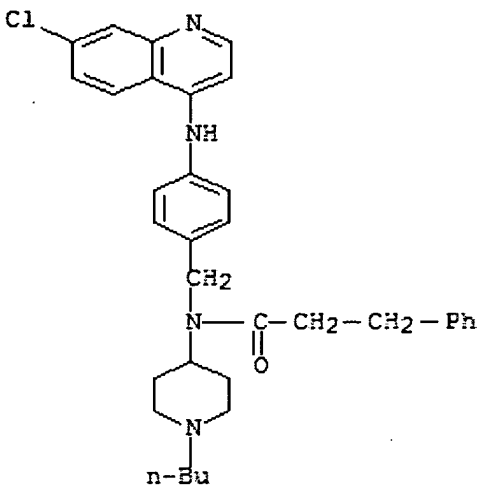
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 8-12, 14, 60 and 82-83 and 85-86 are rejected under 35 U.S.C. 102(b) as being anticipated by Mobilio et al US 5,216,165 A).

Mobilio discloses compounds of Formula I wherein W=O, Z=piperidinyl, R=butyl, X1=CH2, X2=CH2, Y1=CH2, Y2=a bond, Ar1=phenyl and Ar2=C6H4-NH-chloroisoquinoline (see Example 5, column 11). Thus, said claims are anticipated by Mobilio.



Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-14, 53-60 and 79-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomas et al (Tet. Lett. 1997, 38, 5099-5102).

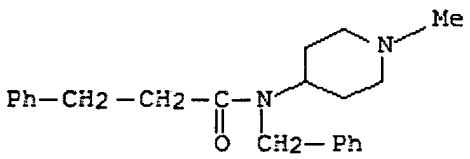
The instant application claims compounds of formula I wherein W=O, Y1=CH2, Y2=CH2, R=CH3, X2=a bond, X1=CH2, Ar1=C6H5 and Ar2=C6H4-CH3 (tolyl).

Scope & Content of Prior Art MPEP 2141.01

Thomas discloses compounds of formula I wherein W=O, Y1=CH2, Y2=CH2, R=CH3, X1=a bond, X2=CH2, Ar1=C6H5 and Ar2=C6H5 (see Table 3).

Differences between Prior Art & the Claims MPEP 2141.02

Thomas differs from the instant invention in that Thomas discloses unsubstituted phenyl which differs from the instant claims at the Ar2 group: a H group versus the Applicant's -CH_3 group, which are considered homologs.

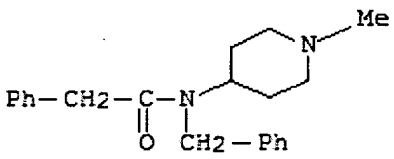


Prima Facie Obviousness, Rational & Motivation MPEP 2142-2413

The MPEP 2144.09 which states: Compounds which are homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH_2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977).

Furthermore, Thomas discloses compounds of formula I wherein W=O, Y1=CH2, Y2=a bond, R=CH3, X2=a bond, X1=CH2, Ar1=C6H5 and Ar2=C6H5 (see Table 3).

Thus said, claims are rendered obvious by Thomas for the previously mentioned reasons.



Double Patenting

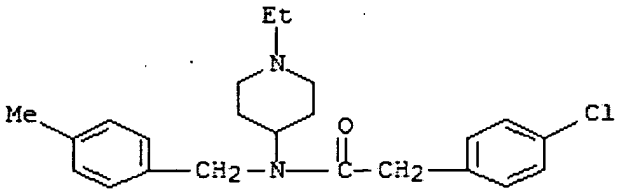
The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

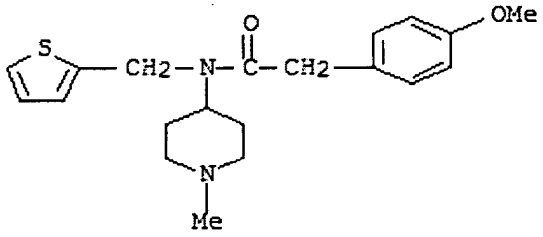
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

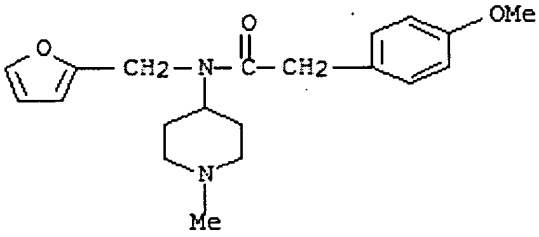
Claims 1-14, 53-60 and 79-88 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of U.S. Patent No.'s 6,756,393 B2 (claims 1-5), 7,253,186 B2 (claims 1-21) and 6,815,458 B2 (claims 1-12). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following.

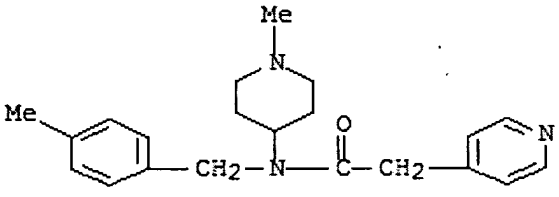
'393, '186 and '458 discloses compounds and pharmaceutical compositions of Formula I as shown below (see entire disclosures). **There are numerous other examples.**



● HCl





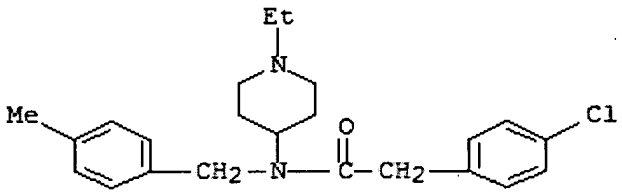


● HCl

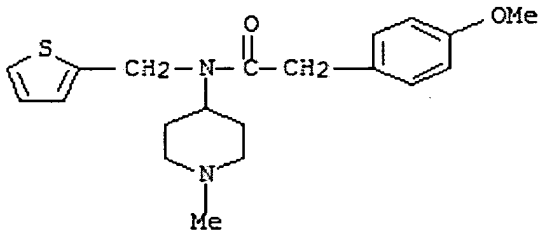
Claims 1-14, 53-60 and 79-88 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No.'s 2006/0194778 A1, 2006/0205722 A1(claims 1-15), 2006/0199818 A1 (claims 1-15), 2006/0094758 A1 (claims 1-14), 2006/0199818 A1 (claims 1-15), 2006/0094758 A1 (claims 1-14) and 2004/0100660 A1 (claims 1-24). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following.

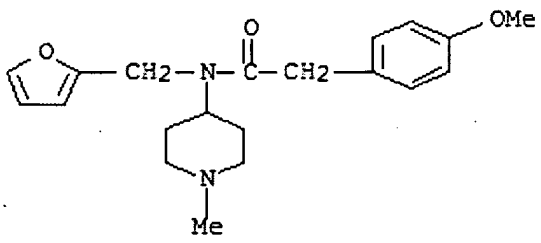
'778, '722, '818, '758, '818, '758 and '660 discloses compounds and pharmaceutical compositions of Formula I as shown below (see entire disclosures).

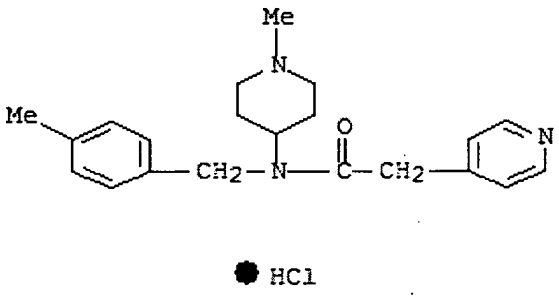
There are numerous other examples.



● HCl







This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

jm

JM

RITA DESAI
PRIMARY EXAMINER
1/22/08